CLAIMS

1. A compound of the general formula (I):

$$B \xrightarrow{Z} N \xrightarrow{X} D \qquad (I)$$

wherein

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R² is hydrogen or C₁₋₆-alkyl,

B is

 R^{38} is hydrogen, $-S(=O)_2-C_{1-6}$ -alkyl or $-C(=O)-C_{1-6}$ -alkyl,

A is a valence bond, -(CR 3 R 4)-, or -(CR 3 R 4)(CR 5 R 6)-,

20 R^1 , R^3 , R^4 , R^5 and R^6 independently are hydrogen or $C_{1\text{-}6}$ -alkyl,

Z is arylene or a divalent radical derived from a 5 or 6 membered heteroaromatic ring containing 1 or 2 heteroatoms selected from nitrogen, oxygen and sulfur,

which may optionally be substituted with one or two groups R^7 and R^8 selected from halogen, -CN, -CF₃, -OCF₃, -NO₂, -OR⁹, -NR⁹R¹⁰ and C₁₋₆-alkyl,

wherein R9 and R10 independently are hydrogen or C1-6-alkyl,

X is

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$$-(CH_{2})_{q}^{-}(CR^{12}R^{13})_{r}^{-}(CH_{2})_{s}^{-} , \qquad -(CR^{12}R^{13})_{r}^{-}(CH_{2})_{s}^{-} ,$$

$$-(CH_{2})_{q}^{-}(CH_{2})_{q}^{-}(CH_{2})_{s}^{-} , \qquad -(CH_{2})_{s}^{-} ,$$

$$-(CH_{2})_{q}^{-}(CH_{2})_{q}^{-} , \qquad -(CH_{2})_{s}^{-} ,$$

$$-(CH_{2})_{q}^{-}(CH_{2})_{s}^{-} ,$$

$$-(CH_{2})_{q}^{-}(CH_{2})_{s}^{-} ,$$

$$-(CH_{2})_{q}^{-}(CH_{2})_{s}^{-} ,$$

$$-(CH_{2})_{q}^{-}(CH_{2})_{s}^{-} ,$$

$$-(CH_{2})_{q}^{-} ,$$

$$-($$

wherein

10 r is 0 or 1,

15

q and s independently are 0, 1, 2 or 3,

 $R^{11},\,R^{12},\,R^{13}$ and R^{14} independently are hydrogen or $C_{\text{1-6}}\text{-alkyl},$

D is

5 wherein

R¹⁵, R¹⁶, R¹⁷ and R¹⁸ independently are

hydrogen, halogen, -CN, -CH₂CN, -CHF₂, -CF₃, -OCF₃, -OCHF₂, -OCH₂CF₃, -OCF₂CHF₂, -S(O)₂CF₃, -SCF₃, -NO₂, -OR²¹, -NR²¹R²², -SR²¹, -NR²¹S(O)₂R²², -S(O)₂NR²¹R²², -S(O)R²¹, -S(O)R²¹, -S(O)₂R²¹, -C(O)NR²¹R²², -OC(O)NR²¹R²², -NR²¹C(O)R²², -CH₂C(O)NR²¹R²², -OCH₂C(O)NR²¹R²², -CH₂OR²¹, -CH₂NR²¹R²², -OC(O)R²¹, -C(O)R²¹ or -C(O)OR²¹,

15 C_{1-6} -alkyl, C_{2-6} -alkenyl or C_{2-6} -alkynyl,

which may optionally be substituted with one or more substituents selected from halogen, - CN, - CF_3 , - NC_2 , - NC_2 , - NR_2 , - NR_2 , and NR_3 and NR_4 .

C₃₋₈-cycloalkyl, C_{4-8} -cycloalkenyl, heterocyclyl, C_{3-8} -cycloalkyl- C_{1-6} -alkyl, C_{3-8} -cycloalkyl- C_{1-6} -alkoxy, C_{3-8} -cycloalkyloxy, C_{3-8} -cycloalkyl- C_{1-6} -alkylthio, C_{3-8} -cycloalkylthio,

 $C_{3\text{-8}}\text{-cycloalkyl-}C_{2\text{-6}}\text{-alkenyl},\ C_{3\text{-8}}\text{-cycloalkyl-}C_{2\text{-6}}\text{-alkynyl},\ C_{4\text{-8}}\text{-cycloalkenyl-}C_{1\text{-6}}\text{-alkyl},\ C_{4\text{-8}}\text{-cycloalkenyl-}C_{2\text{-6}}\text{-alkynyl},\ heterocyclyl-}C_{2\text{-6}}\text{-alkenyl},\ C_{4\text{-8}}\text{-cycloalkenyl-}C_{2\text{-6}}\text{-alkynyl},\ heterocyclyl-}C_{2\text{-6}}\text{-alkynyl},\ aryloxy,\ aryloxycarbonyl,\ aroyl,\ aryl-}C_{1\text{-6}}\text{-alkoxy},\ aryl-}C_{1\text{-6}}\text{-alkyl},\ aryl-}C_{2\text{-6}}\text{-alkynyl},\ heteroaryl-}C_{2\text{-6}}\text{-alkynyl},\ heteroaryl-}$

of which the cyclic moieties optionally may be substituted with one or more substituents selected from halogen, -CN, -CF₃, -OCF₃, -NO₂, -OR²¹, -NR²¹R²² and C₁₋₆-alkyl,

wherein R²¹ and R²² independently are hydrogen, C₁₋₆-alkyl or aryl,

or R²¹ and R²² when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two double bonds,

or two of the groups R^{15} to R^{18} when placed in adjacent positions together may form a bridge $-(CR^{23}R^{24})_a$ -O- $(CR^{25}R^{26})_c$ -O-,

20 wherein

a is 0, 1 or 2,

c is 1 or 2,

25

30

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 R^{23} , R^{24} , R^{25} and R^{26} independently are hydrogen, $C_{1\cdot6}$ -alkyl or fluorine,

 R^{19} and R^{20} independently are hydrogen, C_{1-6} -alkyl, C_{3-8} -cycloalkyl or C_{3-8} -cycloalkyl- C_{1-6} -alkyl,

$$R^{27}$$
 R^{28}
 R^{30}
 R^{31}
 R^{29}
 R^{31}
 R^{31}
 R^{31}
 R^{32}
 R^{31}
 R^{31}
 R^{32}
 R^{31}

wherein

5

R²⁷ and R²⁸ independently are

hydrogen, halogen, -CN, -CF₃, -OCF₃, -OR³², -NR³²R³³, C_{1-6} -alkyl, C_{3-8} -cycloalkyl, C_{4-8} -cycloalkyl, or aryl,

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wherein the aryl group optionally may be substituted with one or more substituents selected from halogen, -CN, -CF₃, -OCF₃, -NO₂, -OR³², -NR³²R³³ and C₁₋₆-alkyl,

wherein

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 $\ensuremath{\mathsf{R}}^{32}$ and $\ensuremath{\mathsf{R}}^{33}$ independently are hydrogen or $C_{\text{1-6}}\text{-alkyl},$ or

R³² and R³³ when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two double bonds,

 R^{29} , R^{30} and R^{31} independently are

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hydrogen, halogen, $-CHF_2$, $-CF_3$, $-OCF_3$, $-OCH_2$, $-OCH_2CF_3$, $-OCF_2CHF_2$, $-SCF_3$, $-OR^{34}$, $-NR^{34}R^{35}$, $-SR^{34}$, $-S(O)R^{34}$, $-S(O)_2R^{34}$, $-C(O)NR^{34}R^{35}$, $-OC(O)NR^{34}R^{35}$, $-NR^{34}C(O)R^{35}$, $-OCH_2C(O)NR^{34}R^{35}$, $-C(O)R^{34}$ or $-C(O)OR^{34}$,

C₁₋₆-alkyl, C₂₋₆-alkenyl or C₂₋₆-alkynyl,

which may optionally be substituted with one or more substituents selected from halogen,

-CN, -CF₃, -OCF₃, -NO₂, -OR³⁴, -NR³⁴R³⁵ and C₁₋₆-alkyl,

 $C_{3\text{-8}}\text{-cycloalkyl},\ C_{4\text{-8}}\text{-cycloalkenyl},\ \text{heterocyclyl},\ C_{3\text{-8}}\text{-cycloalkyl-}C_{1\text{-6}}\text{-alkyl},\ C_{3\text{-8}}\text{-cycloalkenyl-}C_{2\text{-6}}\text{-alkynyl},\ C_{4\text{-8}}\text{-cycloalkenyl-}C_{1\text{-6}}\text{-alkyl},\ C_{4\text{-8}}\text{-cycloalkenyl-}C_{2\text{-6}}\text{-alkynyl},\ \text{heterocyclyl-}C_{1\text{-6}}\text{-alkyl},\ \text{heterocyclyl-}C_{2\text{-6}}\text{-alkenyl},\ \text{heterocyclyl-}C_{2\text{-6}}\text{-alkynyl},\ \text{aryl-}C_{2\text{-6}}\text{-alkynyl},\ \text{aryl-}C_{2\text{-6}}\text{-alkynyl},\ \text{aryl-}C_{2\text{-6}}\text{-alkynyl},\ \text{heteroaryl-}C_{2\text{-6}}\text{-alkenyl}\ \text{or\ heteroaryl-}C_{2\text{-6}}\text{-alkynyl},\ \text{aryl-}C_{2\text{-6}}\text{-alkynyl},\ \text{heteroaryl-}C_{2\text{-6}}\text{-alkynyl},\ \text{h$

of which the cyclic moieties optionally may be substituted with one or more substituents selected from halogen, -CN, -CF₃, -OCF₃, -NO₂, -OR³⁴, -NR³⁴R³⁵ and C₁₋₆-alkyl,

wherein R34 and R35 independently are hydrogen, C1-6-alkyl or aryl,

or R³⁴ and R³⁵ when attached to the same nitrogen atom together with the said nitrogen atom 20 may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two double bonds,

or two of the groups R²⁹, R³⁰ and R³¹ when attached to the same ring carbon atom or different ring carbon atoms together may form a radical -O-(CH₂)₁-CR³⁶R³⁷-(CH₂)₁-O-, -(CH₂)₁-CR³⁶R³⁷-(CH₂)₁- or -S-(CH₂)₁-CR³⁶R³⁷-(CH₂)₁-S-,

wherein

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30 t and I independently are 0, 1, 2, 3, 4 or 5,

R³⁶ and R³⁷ independently are hydrogen or C_{1.6}-alkyl,

as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1, wherein B is

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wherein A and R¹ are as defined in claim 1.

3. A compound according to claim 1, wherein B is

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4. A compound according to claim 1, wherein B is

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5. A compound according to claim 1, wherein B is

wherein R³⁸ is as defined in claim 1.

- 6. A compound according to claim 1, wherein R¹ is hydrogen.
- 7. A compound according to claim 1, wherein A is a valence bond, -CH₂- or -CH₂CH₂-.
- 25 8. A compound according to claim 7, wherein A is -CH₂-.

- 9. A compound according to claim 1 wherein R² is hydrogen.
- 10. A compound according to claim 1, wherein Z is



wherein R⁷ and R⁸ are as defined in claim 1.

10 11. A compound according to claim 10, wherein Z is

12. A compound according to claim 1, wherein X is

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wherein q is 0 or 1, r is 0 or 1, s is 0, 1 or 2, and R^{12} and R^{13} independently are hydrogen or C_{1-6} -alkyl.

- 13. A compound according to claim 12, wherein X is -C(O)NH-, -C(O)NHCH₂-, -C(O)NHCH₂-, -C(O)NHCH₂-, -C(O)CH₂-, -C(
 - 14. A compound according to claim 13, wherein X is -C(O)NH-, $-C(O)NHCH_2-$, $-C(O)NHCH(CH_3)-$, $-C(O)NHCH_2CH_2-$, $-C(O)CH_2-$, $-CH_2-$, -C(O)- or -NHC(O)-.
 - 15. A compound according to claim 14, wherein X is -C(O)NH-.
 - 16. A compound according to claim 1, wherein D is

$$R^{15}$$
 , R^{16} ,

wherein R^{15} , R^{16} , R^{17} , R^{18} , R^{19} and R^{20} are as defined in claim 1.

17. A compound according to claim 16, wherein D is

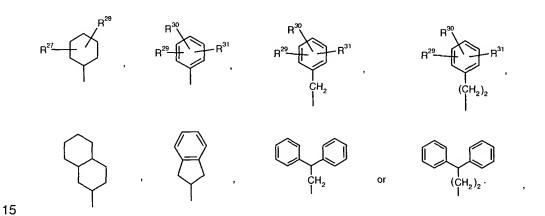
wherein R^{15} , R^{16} and R^{17} are as defined in claim 1.

18. A compound according to claim 16, wherein R¹⁵, R¹⁶ and R¹⁷ independently are hydrogen, halogen, -CN, -NO₂, -CF₃, -OCF₃, -SCF₃, C₁₋₆-alkyl, C₁₋₆-alkoxy, -S-C₁₋₆-alkyl, -C(O)OR²¹, -C(O)R²¹, -C(O)NR²¹R²², -S(O)₂R²¹, -S(O)₂CF₃, -S(O)₂NR²¹R²², C₃₋₈-cycloalkyl or

aryl, or two of the groups R¹⁵, R¹⁶ and R¹⁷ when placed in adjacent positions together form a bridge –(CR²³R²⁴)_a-O-(CR²⁵R²⁶)_c-O-, wherein R²¹ and R²² independently are hydrogen or C₁₋₆-alkyl, and a, c, R²³, R²⁴, R²⁵ and R²⁶ are as defined in claim 1.

- 19. A compound according to claim 18, wherein R¹⁵, R¹⁶ and R¹⁷ independently are hydrogen, -S-C₁₋₆-alkyl, halogen, -CN, -CF₃, -OCF₃ or C₁₋₆-alkoxy, or wherein two of the substituents in adjacent positions form the bridge -CF₂-O-CF₂-O-.
- 20. A compound according to claim 19, wherein R¹⁵, R¹⁶ and R¹⁷ independently are hydrogen, halogen, -S-CH₃, -CF₃ or -OCF₃, or wherein two of the substituents in adjacent positions form the bridge -CF₂-O-CF₂-O-.

21. A compound according to claim 1, wherein E is



wherein R^{27} , R^{28} , R^{29} , R^{30} and R^{31} are as defined in claim 1.

22. A compound according to claim 21, wherein E is

R²⁷ R²⁸

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wherein R^{27} and R^{28} are as defined in claim 1.

- 23. A compound according to claim 21, wherein R^{27} and R^{28} independently are hydrogen, $C_{1.6}$ -alkyl, $C_{3.8}$ -cycloalkyl, $C_{4.8}$ -cycloalkenyl or phenyl.
- 24. A compound according to claim 23, wherein R²⁷ is hydrogen and R²⁸ is C₁₋₆-alkyl,
 C₄₋₈-cycloalkenyl or C₃₋₈-cycloalkyl.
 - 25. A compound according to claim 21, wherein E is

wherein R²⁹, R³⁰ and R³¹ are as defined in claim 1.

26. A compound according to claim 25, wherein E is

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wherein R²⁹, R³⁰ and R³¹ are as defined in claim 1.

27. A compound according to claim 25, wherein R²⁹, R³⁰ and R³¹ independently are

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hydrogen, -CHF₂, -CF₃, -OCF₃, -OCHF₂, -OCH₂CF₃, -OCF₂CHF₂, -SCF₃, -OR³⁴,
 -NR³⁴R³⁵, -SR³⁴, -S(O)R³⁴, -S(O)₂R³⁴, -C(O)NR³⁴R³⁵, -OC(O)NR³⁴R³⁵, -NR³⁴C(O)R³⁵,
 -OCH₂C(O)NR³⁴R³⁵, -C(O)R³⁴ or -C(O)OR³⁴,

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C₁₋₆-alkyl, C₂₋₆-alkenyl or C₂₋₆-alkynyl,

which may optionally be substituted with one or more substituents selected from halogen, -CN, -CF₃, -OCF₃, -NO₂, -OR³⁴, -NR³⁴R³⁵ and C_{1-6} -alkyl,

• C₃₋₈-cycloalkyl or C₄₋₈-cycloalkenyl,

which may optionally be substituted with one or more substituents selected from halogen, -CN, -CF₃, -OCF₃, -NO₂, -OR³⁴, -NR³⁴R³⁵ and C₁₋₆-alkyl,

5 wherein R³⁴ and R³⁵ independently are hydrogen, C₁₋₆-alkyl or aryl,

or R³⁴ and R³⁵ when attached to the same nitrogen atom together with the said nitrogen atom may form a 3 to 8 membered heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, and optionally containing one or two double bonds.

- 28. A compound according to claim 27, wherein R²⁹, R³⁰ and R³¹ independently are
- hydrogen, C₁₋₆-alkoxy, -CF₃, -OCF₃ or -NR³⁴R³⁵, wherein R³⁴ and R³⁵ are as defined in
 claim 1, or
 - C₁₋₆-alkyl, C₃₋₈-cycloalkyl or C₄₋₈-cycloalkenyl, which are optionally substituted as defined in claim 1.
- 20 29. A compound according to claim 28, wherein R²⁹, R³⁰ and R³¹ independently are
 - hydrogen or
 - C₁₋₆-alkyl, C₃₋₈-cycloalkyl or C₄₋₈-cycloalkenyl, which are optionally substituted as defined in claim 1.
 - 30. A compound according to claim 29, wherein R^{29} , R^{30} and R^{31} independently are hydrogen, C_{1-6} -alkyl, C_{3-8} -cycloalkyl or C_{4-8} -cycloalkenyl.
- 31. A compound according to claim 30, wherein R^{29} and R^{31} are both hydrogen and R^{30} is C_{1-6} -alkyl, C_{3-8} -cycloalkyl or C_{4-8} -cycloalkenyl.
 - 32. A compound according to claim 31, wherein R^{29} and R^{31} are both hydrogen and R^{30} is C_{1-6} -alkyl.

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33. A compound according to claim 1 of the general formula (la):

- wherein R¹, R², R³, R⁴, R⁷, R⁸, X, D and E are as defined in claim 1 or in any one of the preceding claims.
 - 34. A compound according to claim 33, wherein R¹, R², R³, R⁴, R⁷ and R⁸ are hydrogen.
- 10 35. A compound according to claim 1 of the general formula (lb):

wherein R², R⁷, R⁸, X, D and E are as defined in claim 1 or in any one of the preceding claims.

36. A compound according to claim 1 of the general formula (Ic):

wherein R², R⁷, R⁸, X, D and E are as defined in claim 1 or in any one of the preceding claims.

37. A compound according to claim 1 of the general formula (Id):

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wherein R², R⁷, R⁸, R³⁸, X, D and E are as defined in claim 1 or in any one of the preceding claims.

38. A compound according to claim 35, wherein R², R⁷ and R⁸ are hydrogen.

- 39. A compound according to claim 1, wherein said compound has an IC₅₀ value of no greater than 5 μ M as determined by Glucagon Binding Assay (I) or Glucagon Binding Assay (II).
- 40. A compound according to claim 39, wherein said compound has an IC_{50} value of less than 1 μ M as determined by Glucagon Binding Assay (I) or Glucagon Binding Assay (II).
- 41. A compound according to claim 1, wherein said compound is an agent useful for the treatment and/or prevention of an indication selected from the group consisting of hypergly-cemia, impaired glucose tolerance, Type 2 diabetes, Type 1 diabetes and obesity.
 - 42. A compound according to any one of the claims 1 to 41 for use as a medicament.
 - 43. A pharmaceutical composition comprising at least one compound according to claim 1 together with one or more pharmaceutically acceptable carriers or excipients.
- 44. A pharmaceutical composition according to claim 43 in unit dosage form, said composition comprising from about 0.05 mg to about 1000 mg of the compound according to claim 1.
 - 45. Use of a compound according to any one of the claims 1 to 41 for the preparation of a medicament for the treatment and/or prevention of disorders or diseases, wherein a glucagon antagonistic action is beneficial.

- 46. Use of a compound according to any one of the claims 1 to 41 for the preparation of a medicament for the treatment and/or prevention of glucagon-mediated disorders and diseases.
- 5 47. Use of a compound according to any one of the claims 1 to 41 for the preparation of a medicament for the treatment and/or prevention of hyperglycemia.
 - 48. Use of a compound according to any one of the claims 1 to 41 for the preparation of a medicament for lowering blood glucose in a mammal.
 - 49. Use of a compound according to any one of the claims 1 to 41 for the preparation of a medicament for the treatment and/or prevention of IGT.
- 50. Use of a compound according to any one of the claims 1 to 41 for the preparation of a medicament for the treatment and/or prevention of Type 2 diabetes.
 - 51. Use according to claim 50 for the preparation of a medicament for the delaying or prevention of the progression from IGT to Type 2 diabetes.
- 52. Use according to claim 50 for the preparation of a medicament for the delaying or prevention of the progression from non-insulin requiring Type 2 diabetes to insulin requiring Type 2 diabetes.
- 53. Use of a compound according to any one of the claims 1 to 41 for the preparation of a medicament for the treatment and/or prevention of Type 1 diabetes.
 - 54. Use of a compound according to any one of the claims 1 to 41 for the preparation of a medicament for the treatment and/or prevention of obesity.
- 30 55. Use according to any one of the claims 45 to 54 in a regimen which comprises treatment with a further antidiabetic agent.
 - 56. Use according to any one of the claims 45 to 55 in a regimen which comprises treatment with a further antiobesity agent.

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- 57. Use according to any one of the claims 45 to 56 in a regimen which additionally comprises treatment with an antihypertensive agent.
- 58. A method for the treatment or prevention of disorders or diseases, wherein a glucagon
 antagonistic action is beneficial, said method comprising administering to a subject in need thereof an effective amount of a compound according to claim 1.
 - 59. The method according to claim 58, wherein the effective amount of the compound is in the range of from about 0.05 mg to about 2000 mg per day.
 - 60. The method according to claim 58, wherein the effective amount of the compound is in the range of from about 0.1 mg to about 1000 mg per day.
- 61. The method according to claim 58, wherein the effective amount of the compound is in the range of from about 0.5 mg to about 500 mg per day.
 - 62. A method for the treatment or prevention of glucagon-mediated disorders and diseases, said method comprising administering to a subject in need thereof an effective amount of a compound according to claim 1.
 - 63. A method for the treatment or prevention of hyperglycemia, said method comprising administering to a subject in need thereof an effective amount of a compound according to claim 1.
- 25 64. A method for lowering blood glucose in a mammal, said method comprising administering to said mammal in need thereof an effective amount of a compound according to claim 1.
 - 65. A method for the treatment or prevention of impaired glucose tolerance, said method comprising administering to a subject in need thereof an effective amount of a compound according to claim 1.
 - 66. A method for the treatment or prevention of Type 2 diabetes, said method comprising administering to a subject in need thereof an effective amount of a compound according to claim 1.

- 67. A method for delaying or preventing the progression from impaired glucose tolerance to Type 2 diabetes, said method comprising administering to a subject in need thereof an effective amount of a compound according to claim 1.
- 5 68. A method for delaying or preventing the progression from non-insulin requiring Type 2 diabetes to insulin requiring Type 2 diabetes, said method comprising administering to a subject in need thereof an effective amount of a compound according to claim 1.
- 69. The method according to claim 58, said method further comprising administering to said subject an antidiabetic agent.
 - 70. The method according to claim 58, said method further comprising administering to said subject an antiobesity agent.
- 15 71. The method according to claim 58, said method further comprising administering to said subject an antihypertensive agent.
 - 72. A pharmaceutical composition according to claim 43 in unit dosage form, said composition comprising from about 0.1 mg to about 500 mg of the compound according to claim 1.
 - 73. A pharmaceutical composition according to claim 43 in unit dosage form, said composition comprising from about 0.5 mg to about 200 mg of the compound according to claim 1.
- 74. A compound according to claim 39, wherein said compound has an IC₅₀ value of less than 500 nM as determined by Glucagon Binding Assay (I) or Glucagon Binding Assay (II).
 - 75. A compound according to claim 39, wherein said compound has an IC_{50} value of less than 100 nM as determined by Glucagon Binding Assay (I) or Glucagon Binding Assay (II).